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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,610	09/16/2003	Charles Wilson	23239-538 (ARC-38)	5499

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
11/19/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,610	WILSON ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *127-137* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *127-137* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 13 October 2010.

Claims 1-126 have been cancelled.

Claims 127-137 are pending and currently examined.

WITHDRAWN OBJECTIONS

The objection to the title is withdrawn in view of Applicant's argument.

The objection to the abstract is withdrawn in view of Applicant's amendment.

Specification

The objection to the specification is maintained because simply deleting the trademark symbol does not change the fact that the acronym "SELEX" is a trademark, regardless of what its full name is. MPEP §608.01(v) requires the term be capitalized wherever it appears and be accompanied by the generic terminology, such as an aptamer selection process.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 127-130, 136 and 137 under 35 U.S.C. §103(a) as being unpatentable over Lupold *et al*. (US 6,933,114 B2, filed 16 October 2001) is maintained.

The instant claims are directed to a method for identifying an aptamer regulator comprising:

a) providing a target and a target partner that do not bind to each other in the absence of an aptamer regulator;

b) contacting a mixture of nucleic acids with the target and the target partner under conditions that disfavor efficient binding between the target and the target partner;

c) partitioning nucleic acids bound to a target-target partner (T/TP) complex from unbound nucleic acids; and

d) retaining the nucleic acids bound to the T/TP complex, thereby identifying an aptamer that binds to a target, wherein binding of the aptamer to the target increases the binding affinity of the target for the target partner relative to when the target is not bound by the aptamer regulator.

The claim limitation of binding between a "target" and "target partner" reads on any interaction between a target and another molecule. The claim limitation of "aptamer regulator" reads on a nucleic acid ligand.

Claims 128 and 129 further limit the mixture of nucleic acids to a target-specific and diversified pool. Claim 130 further limits the target partner to be immobilized. Claim 136 further comprises the step of amplifying the retained nucleic acids and

repeating steps a) to d). Claim 137 further comprises the step of screening the retained nucleic acids for a desired functional activity.

Lupold *et al.* discloses a basic method for identifying an aptamer comprising the steps of contacting a mixture of nucleic acids with the target, partitioning nucleic acids bound to target from the unbound nucleic acids, amplifying the retained nucleic acids (col. 8, lines 3-13), and repeating the partitioning/amplifying steps (col. 10, lines 22-52). The candidate mixture is a mixture of nucleic acids of differing sequences with fixed sequences surrounding a randomized region (col. 10, lines 8-21). The fixed sequences can mimic a sequence known to bind to the target (col. 10, line 13-14), which renders the mixture of nucleic acids target-specific. Such randomized sequences are known in the art to render a diversified pool of nucleic acids as Lupold et al. also discloses the diversity of the structures employed by an aptamer library (col. 4, lines 43-44). Lupold *et al.* further discloses the step of screening the retained or identified nucleic acids for a desired functional activity such as the ability to inhibit NAALADase enzyme activity (col. 15, lines 63-64).

Lupold *et al.* does not explicitly disclose a target partner and the desired functional activity of the aptamer binding to the target to increase the binding affinity of the target for the target partner relative to the unbound target.

However, Lupold *et al.* suggests that the basic aptamer selection method has been modified to achieve specific objectives (col. 10, lines 53-54) and further explicitly

suggests nucleic acid ligands, often referred to as "aptamers," having desirable functions on a target including binding of the target, catalytically changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, facilitating the reaction between the target and another molecule (col. 7, lines 53-61), which means the same as the claim limitation of "an aptamer regulator that binds to a target wherein the binding increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer regulator" in the instant claims.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Lupold *et al*. so as to further include, in each method step, a target partner that does not bind the target without an agonist like the aptamer regulator. One having ordinary skill in the art would have been motivated to make such a modification to select for aptamers with the desirable functions of binding of the target, catalytically changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, and facilitating the reaction between the target and another molecule, as per the suggestion of Lupold *et al*.

Although Lupold *et al*. does not disclose immobilizing a target partner, Lupold *et al*. discloses immobilizing the target on a solid support (col. 8, lines 62-67 continued on to col. 9, line 6). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Lupold *et al*. so as to immobilize

the target partner rather than the target. One having ordinary skill in the art would have been motivated to make such a modification for the convenience of partitioning nucleic acid-bound target that is bound to the target partner.

There would have been a reasonable expectation of success, given the variety of modifications to the basic method that are routinely practiced by one of ordinary skill in the art, as disclosed by Lupold *et al.* (col. 10, lines 53 to col. 11, line 54). Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that the Lupold does not disclose a variation or modification of SELEX to identify an aptamer (*i.e.*, aptamer regulators) that facilitate the reaction between a target and another molecule and that modifications to a method can not be obvious based upon a desirable action of an aptamer, as there is no nexus between the desirable action of the aptamer and steps to identify such an aptamer. In addition, applicants' claimed method uses conditions that disfavor binding, which is the opposite of what is disclosed or suggested in Lupold.

In response to Applicant's argument regarding the missing nexus between the desirable action and the steps to identify an aptamer, it is respectfully submitted that

the applicants' argument seems to be based on the lack of *ipsis verbis* recitation of the claimed method steps in the cited prior art.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the rationale to support the present rejection under 35 U.S.C. 103(a) is some teachings, suggestion, or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention. The prior art discloses the method comprising contacting nucleic acid mixture with the targets which the aptamer is intended to bind and screening the bound nucleic acids for the desired functional activity. Since the prior art also clearly suggests the modification to select for the desired functional activity of binding a target and increasing it's affinity for a target partner, albeit not literally recited, by suggesting the desired functions of "binding of the target, catalytically changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, facilitating the reaction between the target and another molecule." The "another molecule" would be the "target partner" in the instant case. The "reacting with the target in a way which modifies/alters the target or the functional activity of the target" would be the "binding of the aptamer regulator to the target increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer regulator" as recited in the presently rejected claims.

In response to Applicant's argument that there is no suggestion or motivation in any of the cited documents, it is respectfully pointed out that the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved." *Kotzab*, 217 F.3d at 1370, 55 USPQ2d at 1317. The suggestion or motivation to modify the reference does not have to be in the references themselves. See MPEP §2142.

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the

knowledge of one skilled in the art." *Motorola, Inc. v. Interdiqital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Applicant's assertion that the claimed method conditions disfavoring binding is the opposite of what is disclosed or suggested in Lupold lacks evidentiary basis and supportive reasons. Applicant never clearly points out the "conditions" that disfavor binding between the target and the target partner. There is no objective evidence comparing the claimed method steps with the prior art modifications to the SELEX to identify an aptamer that binds to the target, catalytically changes the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, and facilitating the reaction between the target and another molecule (col. 7, lines 55-61). Such desired actions are the same as the functional characteristics that are required for the instantly claimed aptamer regulator. That is, the claimed aptamer regulator is required to bind to the target and catalytically change the target shape so that the target partner can bind the target with increased affinity. Therefore, the prior art modification of the SELEX to identify "an aptamer that binds to the target, catalytically changes the target, reacting with the target in a way which modifies/alters the target or

the functional activity of the target, and facilitating the reaction between the target and another molecule" would arrive at the instantly claimed method of contacting nucleic acid mixture with both a target and a target partner that do not bind each other in the absence of an aptamer regulator.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection of claims 131-133 and 135 under 35 U.S.C. §103(a) as being unpatentable over Lupold *et al*. (US 6,933,114 B2, filed 16 October 2001) in view of Geiger *et al*. (1996, of record in IDS filed 16 April 2010) is maintained.

The instant invention further comprises: (1) a negative selection prior to step (a) comprising partitioning and discarding nucleic acids bound to the target partner; and (2) the step of removing the retained nucleic acids from the target-target partner (T/TP) complex by eluting the nucleic acids with free excess target.

The disclosure of Lupold *et al*. is set forth above. Lupold *et al*. does not disclose the prior step of negative selection or the step of eluting the nucleic acids with excess free target.

Geiger *et al*. discloses the step (1) of a negative selection with a non-desired target in which the pool of nucleic acids are partitioned and washed away with a non-desired target, citrulline, prior to the selection of arginine-specific aptamers; and the

step (2) of elution of arginine-specific aptamers with an excess of free target, a 20 mM solution of arginine (page 1030, right column, see the passage entitled "Selections").

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the selection method disclosed by Lupold *et al.* so as to further include the step of negative selection with a non-desired target, such as the target partner in the instant case, and the step of eluting the nucleic acids with free excess target, as suggested by Geiger *et al.*, with a reasonable expectation of success because this selection scheme and this elution technique are routine optimizations known in the art of aptamer selection. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that the Geiger method does not disclose or suggest binding target, target partner and nucleic acids under conditions that disfavor binding and that Geiger does not even contemplate aptamer regulators or methods for identifying aptamer regulators.

The Geiger reference, however, is only cited to render obvious the negative selection step and the excess target elution step. The primary reference, Lupold, renders obvious the other claim elements for reasons set forth above.In response to

applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The rejection of claims 133 and 134 under 35 U.S.C. §103(a) as being unpatentable over Lupold *et al.* (US 6,933,114 B2, filed 16 October 2001) in view of Firer *et al.* (30 October 2001) is maintained.

The instant invention further comprises the step of removing the retained nucleic acids from the T/TP complex by eluting with an agonist competitor to the target.

The disclosure of Lupold *et al.* is set forth above. Lupold *et al.* does not disclose eluting the nucleic acids with an agonist competitor to the target.

Firer *et al.* discloses the strategy of competitive elution with excess ligands from a target molecule immobilized to a resin in a chromatography column (page 438, third complete paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the selection method disclosed by Lupold *et al.* so as to further include the step of eluting the nucleic acids with an agonist competitor to displace the nucleic acid ligands bound to the target, as suggested by Firer *et al.*, with a reasonable expectation of success because competitive elution, an elution technique using a competitor for the same binding site on the target to remove the bound ligand, is a routine procedure that has been demonstrated in the art to separate the ligand

from the target protein, as disclosed in Firer *et al*. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that Firer discloses competitive elution with excess ligand, and not an agonist competitor to the target, and that an agonist competitor would be a molecule that is different from the ligand to a target.

Examiner respectfully disagrees with Applicant's assertion regarding the difference between an agonist competitor and a ligand. Applicant's argument is only based on the difference in the words but not on any objective evidence. A ligand, by its definition in a dictionary, is anything that binds a target. The generic word "ligand" includes the more specific term "agonist competitor," which not only binds but also activates and competes with another agonist for binding to the target. So long as the technology of competitive elution is known, one of ordinary skill in the art would know how to apply the known method to any other known elements in the art such as an agonist. When the nucleic acid pool/mixture is being selected for an agonist to the target, then its competitor would be obviously termed "agonist competitor." Therefore, the modification impliedly suggested by Firer *et al*. can be reasoned from knowledge generally available to one of ordinary skill in the art. Furthermore, as already set forth

above, the modification of the SELEX to select for the desired activity of an agonist that increases the target affinity for its partner is explicitly suggested by Lupold *et al*. (col. 7, lines 53-61) when disclosing the desired functions of "binding of the target, catalytically changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, facilitating the reaction between the target and another molecule."

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas, can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Zachariah Lucas/
Supervisory Patent Examiner, Art Unit 1648